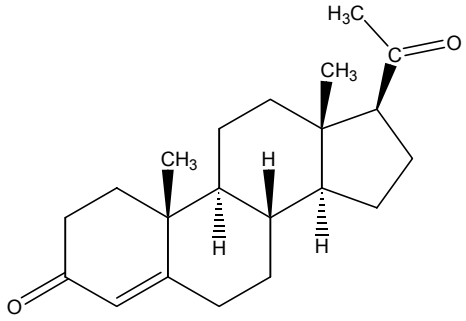
PROGESTERONE
CAS No. 57-83-0
First Listed in the *Fourth Annual Report on Carcinogens*



CARCINOGENICITY

Progesterone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC S.4, 1982). When progesterone was implanted subcutaneously, mammary carcinomas were induced at a significantly earlier age and at a higher incidence in female mice. Long-term subcutaneous implants induced ovarian granulosa cell tumors or endometrial stromal sarcomas in female mice (IARC V.6, 1974; IARC V.21, 1979). Subcutaneous injections of progesterone induced increased incidences of mammary tumors in adult female mice and lesions of the vaginal or cervical epithelia and genital tract lesions in newborn female mice. Hyperplastic alveolar-like nodules and other dysplasias were also induced in female neonatal mice (IARC V.21, 1979). Long-term subcutaneous injections in female dogs induced endometrial hyperplasia, inhibition of ovarian development, marked mammary hyperplasia, and some fibroadenomatous nodules of the mammary gland (IARC V.21, 1979; IARC S.4, 1982).

Female mice injected subcutaneously with progesterone showed decreased latent periods for the induction of mammary tumors by 3-methylcholanthrene. Ovariectomized female mice receiving injections of progesterone developed sarcomas of the uterine horn when given an intrauterine implant of 3-methylcholanthrene and developed increased incidences of squamous cell carcinomas of the cervix or vagina when treated intravaginally with 7,12-dimethylbenz[*a*]anthracene (IARC V.6, 1974; IARC V.21, 1979). Local applications of 3-methylcholanthrene and subcutaneous implantations of progesterone induced increased incidences of vaginal-cervical invasive squamous cell carcinomas in female mice (IARC V.21, 1979). Rats receiving subcutaneous or intramuscular injections of progesterone had decreased latent periods and/or increased incidences of mammary tumors induced by oral administration of 3-methylcholanthrene or 7,12-dimethylbenz[*a*]anthracene, but only when the known carcinogens were administered first. An increased incidence of mammary tumors was induced in female rats fed 2-acetylaminofluorene in the diet and injected intramuscularly with progesterone. Newborn female rats receiving a subcutaneous injection of progesterone and a subsequent intragastric instillation of 7,12-dimethylbenz[*a*]anthracene developed increased incidences of mammary adenocarcinomas (IARC V.21, 1979).

There are no data available to evaluate the carcinogenicity of progesterone in humans (IARC S.4, 1982; IARC V.21, 1979; IARC V.6, 1974).

PROPERTIES

Progesterone is a crystalline solid at room temperature. It occurs in two forms that are readily interconvertible: white orthorhombic prisms and white orthorhombic needles. It is practically insoluble in water; sparingly soluble in vegetable oils; and soluble in ethanol, arachis oil, chloroform, diethyl ether, ethyl oleate, light petroleum, acetone, dioxane, and concentrated sulfuric acid. It is commercially available as a grade containing 98%-102% active ingredient on a dried basis, with ≤ 3% foreign steroids and other impurities. It is sensitive to light.

USE

Progesterone is a naturally occurring steroidal hormone found in a wide variety of tissues and biological fluids. It is secreted by the ovary in normal adult cycling females, by the placenta in pregnant females, and by the adrenal cortex. It is essential for the normal functioning of the uterine lining, for the development of mammary glands, and support of pregnancy through parturition (Prosser, 1973). Progesterone is used in medicine to treat secondary amenorrhea and dysfunctional uterine bleeding. It has also been used to treat female hypogonadism, dysmenorrhea and premenstrual tension, habitual and threatened abortion, preeclampsia and toxemia of pregnancy, mastodynia, uterine fibroma, and neoplasms of the breast and endometrium. Progesterone embedded in an intrauterine device is used for contraception. In veterinary medicine, progesterone is used to control habitual abortion and to delay estrus and ovulation in cattle, swine, and dogs (IARC V.21, 1979).

PRODUCTION

Progesterone is a naturally occurring steroid hormone produced endogenously by all mammalian species. The production rate in humans ranges from 0.15 mg/24 hr in prepubertal boys to 19.58 mg/24 hr in normal adult cycling females (Tagatz & Gurpide, 1973). The USITC identified one producer of progesterone for 1988, but no production data were reported (USITC, 1989). Chem Sources International identified two domestic suppliers of progesterone for 1988 and 1989 (Chem Sources, International, 1988). In 1986, one U.S. company produced an undisclosed volume of progesterone (USITC, 1987). The 1979 TSCA Inventory identified one importer of progesterone in 1977, but data on the amount of U.S. imports and exports of progesterone were not available (TSCA, 1979). In 1975, U.S. production of 13 estrogen and progestin substances, including progesterone, amounted to 23,100 lb. Before U.S. governmental restrictions in 1973, total U.S. sales of progesterone for use in human medicine were estimated to have been < 110 lb annually (IARC V.6, 1974).

EXPOSURE

The primary routes of potential exogenous human exposure to progesterone are ingestion, injection of medications containing the compound, implantation, dermal contact, and inhalation. Injection dosages range from 2 to 50 mg, either in single or multiple administrations. Progesterone embedded in an intrauterine contraceptive device is a potential route of exposure to a limited population. Human placental extracts, of which progesterone is believed to be the main constituent, have been used in preparations for cosmetic use (at levels of 0.1%-1.0%), hair conditioners, shampoos, and grooming aid tonics (< 0.1%) (IARC V.21, 1979). Potential consumer exposure through dermal contact could occur from use of these cosmetics. FDA reported that progesterone has been detected in cow's milk at concentrations of 1-30 ng/ml and in milk products at up to 300 μg/kg (in butter). It has also been found to occur naturally in certain

plant species (IARC V.21, 1979). Animal meat may contain an average of 0.33 mg progesterone/kg if the animal was treated with a progesterone implant. Consumers could potentially be exposed to progesterone by ingesting these food products. Potential occupational exposure to progesterone may occur through inhalation and dermal contact during its production or formulation into pharmaceuticals. A joint investigation of an oral contraceptive plant, conducted by NIOSH and CDC, found evidence of hyperestrogenism in both male and female workers and wide variations in air sample concentrations of estrogen and progesterone (Drug Cosmet. Ind., 1977). The National Occupational Exposure Survey (1981-1983) indicated that 287 workers, including 54 women, potentially were exposed to progesterone (NIOSH, 1984). This estimate was derived from observations of the actual use of the compound. The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 22,963 workers were potentially exposed to progesterone in the workplace in 1970 (NIOSH, 1976).

REGULATIONS

Progesterone is not regulated by EPA because it is used as a pharmaceutical and in low quantities relative to other chemicals. However, there may be a small pollution problem relative to hospital wastes. FDA regulates progesterone under the Food, Drug, and Cosmetic Act (FD&CA) as a prescription drug approved for human use. FDA has ruled that progesterone must carry a warning label for patients and physicians concerning use, risks, and contraindications. FDA also requires that no residues of progesterone be found in the uncooked edible tissues of lamb and steer. OSHA regulates progesterone as a chemical hazard in laboratories and under the Hazard Communication Standard. Regulations are summarized in Volume II, Table B-126.